PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Cognitive and neuroimaging outcomes in individuals with benign and low-grade brain tumors receiving radiotherapy: a protocol for a prospective cohort study
AUTHORS	Hardy, Sara; Finkelstein, Alan J.; Tivarus, Madalina; Culakova, Eva; Mohile, Nimish; Weber, Miriam; Lin, Edward; Zhong, Jianhui; Usuki, Kenneth; Schifitto, Giovanni; Milano, Michael; Janelsins-Benton, MC

VERSION 1 – REVIEW

REVIEWER	Gameiro-Santos, Rita Centro Hospitalar Barreiro Montijo EPE, Medical Oncology
REVIEW RETURNED	02-Aug-2022

GENERAL COMMENTS	On page 4; line 52: What do you mean when you say novel therapeutics? Are they the same as you say in the discussion & conclusion line 30 “techniques such as intensity modulated radiation therapy and proton therapy”? It would enrich the “novelty and innovation” section if you specified those novel therapeutics as it would be clear they already exist and would be used more often in specialized cases of subjects who are at risk, possibly identified by your study. On page 5, line 33: What do you classify as low grade glioma? The new WHO 2016 classification and its revised version in 2021 does not include that classification. Do you mean IDH-mutant Astrocytoma Grade 2? Do you include any malignant tumours? Please clarify inclusion criteria for malignant tumours. On page 5, line 36: Chemotherapy prior to enrolment is permitted. How are you planning to differentiate the symptoms of chemobrain? It has not the same fisiopathology as RICD but the cognitive tests you will run may be affected by it so you will have mixed results. Shouldn’t you exclude chemo patients?

REVIEWER	Laprie, Anne Institut Universitaire du Cancer de Toulouse Oncopole CHU Toulouse
REVIEW RETURNED	27-Dec-2022

GENERAL COMMENTS	This manuscript is clear and well- written. It describes an ongoing prospective protocol addressing a very interesting question : does RT affect network typology and microstructural integrity ? this prospective study is well designed to answer the question although there are some expected limitations. there is only one sentence on limitations in the dedicated paragtraph "A significant limitation is heterogeneity of tumor type and laterality in patient population.However, excluding high grade tumors minimizes this limitation as much as possible while still allowing the study to be feasible at a single institution." I would add other limitations as : range of ages, variety of benign and low grade tumors which will have very different sizes and localisations. variety of radiotherapy techniques). in the abstract, the number of patients expected for inclusion should be mentioned. the NCT number should also be specified , I guess it is NCT04390906 ; the types of ROI that will be analyzed should be listed or wil the ROI only be nodes ? Won't there be correlation with doses to whole brain or hippocampi?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Comments to the Author:

On page 4; line 52: What do you mean when you say novel therapeutics? Are they the same as you say in the discussion & conclusion line 30 “techniques such as intensity modulated radiation therapy and proton therapy”? It would enrich the “novelty and innovation” section if you specified those novel therapeutics as it would be clear they already exist and would be used more often in specialized cases of subjects who are at risk, possibly identified by your study.

Thank you, we have clarified what we meant by novel therapeutics. The sentence on page 4 has been revised as follows:

“Whole brain metrics such as functional connectivity may provide early identification of participants who are at risk of decline and can be targeted with novel therapeutics, either by using advanced RT techniques to improve RT plans or use of radioprotective pharmaceuticals.”

On page 5, line 33:

What do you classify as low grade glioma? The new WHO 2016 classification and its revised version in 2021 does not include that classification. Do you mean IDH-mutant Astrocytoma Grade 2? Do you include any malignant tumours? Please clarify inclusion criteria for malignant tumours.

That is an excellent point and this has been clarified. We have excluded grade 3 and 4 astrocytoma and oligodendroglioma and IDH WT glioblastoma in order to minimize variation in tumor biology and amount of normal tissue infiltration from the tumor. This also allows us to focus on patients who are expected to be long-term survivors.

The sentence on page 5 has been revised as follows:

“Key inclusion criteria include 1) age ≥18-years; 2) patients with benign or low-grade brain tumors including grade 2 IDH-mutant astrocytoma, grade 2 oligodendroglioma, grade 1 and 2 meningiomas, vestibular schwannomas, pituitary adenomas, craniopharyngiomas, hemangiopericytomas, or other benign or low-grade brain tumors; 3) planned to receive either

conventional or hypofractionated RT; 4) no contraindication to gadolinium-enhanced MRI. Surgical excision and/or chemotherapy prior to enrollment is permitted."

On page 5, line 36:
Chemotherapy prior to enrollment is permitted. How are you planning to differentiate the symptoms of chemobrain? It has not the same physiopathology as RICD but the cognitive tests you will run may be affected by it so you will have mixed results. Shouldn't you exclude chemo patients?

While we agree that receipt of chemotherapy is a potential confounder, this was not made an exclusion in order to ensure sufficient patients can be enrolled in a single institution study. This is a limitation of the study, which has been added to the Limitations section on page 2:

"Heterogeneity of the patient population including tumor type, size, and location, radiation techniques, patient clinical factors including age, other cancer treatments including chemotherapy and surgery allows us to increase generalizability of results; however, these factors will be examined in analysis for contributing effects on cognitive function."

Reviewer: 2
Comments to the Author:
This manuscript is clear and well-written. It describes an ongoing prospective protocol addressing a very interesting question: does RT affect network typology and microstructural integrity?

This prospective study is well designed to answer the question although there are some expected limitations. There is only one sentence on limitations in the dedicated paragtraph: "A significant limitation is heterogeneity of tumor type and laterality in patient population. However, excluding high grade tumors minimizes this limitation as much as possible while still allowing the study to be feasible at a single institution." I would add other limitations as: range of ages, variety of benign and low grade tumors which will have very different sizes and localisations, variety of radiotherapy techniques).

Thank you, we agree that these are additional possible limitations and have included this in the strengths and limitations section on page 2 per reviewer the reviewer comment above.

In the abstract, the number of patients expected for inclusion should be mentioned.
the NCT number should also be specified, I guess it is NCT04390906;

That is correct, this information has been added to the abstract.

The types of ROI that will be analyzed should be listed or will the ROI only be nodes ? Won't there be correlation with doses to whole brain or hippocampi?
Thank you for this excellent question. We have added additional sentences to clarify this in the paper.

We will use autosegmented structures derived as described in the protocol as ROIs. We anticipate that there will be correlation between radiation doses to ROIs (including hippocampi and whole brain) and will examine the relationship between these measures and utilize appropriate statistics such as a mixed effect regression model that can address correlated variables.

This sentence was added on page 9: "ROIs will include whole brain gray and white matter, cerebral hemispheres and subcortical gray matter (hippocampus, amygdala, caudate, putamen, thalamus, nucleus basalis of Meynert), as well as white matter tracts including cingulum, fornix, parahippocampal white matter, and corpus callosum."

This sentence was revised on page 11: "Multivariate mixed effect regression models will be used to evaluate the relationships of cognitive tests at 6-month and 12-month visits with RT dose to ROIs known to be instrumental in the specific cognitive domain adjusting for the baseline cognitive test, imaging parameters, age, gender, tumor laterality, and tumor type."

Reviewer: 1
Competing interests of Reviewer: No competing interests

Reviewer: 2
Competing interests of Reviewer: No